REMARKS

Claims 154-160 were pending. Claim 157 is amended, and new claim 161 is added. Support for the amended and new claims are found throughout the specification, and therefore it is believed that no new matter is added. Claim 160 is canceled herewith. Claims 154-159 and 161 are pending. No claim is allowed.

Priority Claims to U.S. Provisional Application Serial No. 60/044,693

The Examiner alleges that the method of claim 157 which recites all of the particular antibodies and combinations is not entitled to priority of U.S. Provisional Application Serial No. 60/044,693, filed July 26, 1995. Applicant traverses this denial of priority.

Applicant submits that claim 157 as amended is fully supported by the disclosure in the cited provisional application. *See* U.S. Provisional Application Serial No. 60/044,693 at pages 12-13. This disclosure clearly conveys to the skilled artisan possession of the claimed invention, and therefore the claimed methods are rightly entitled to the priority date of July 26, 1995. *See* MPEP § 2163(II)(A)(3)(b) ("To assert priority, an applicant must clearly convey to the skilled artisan possession of the claimed invention.").

In view of the above, Applicant respectfully submits that the claimed methods are entitled to the priority date of July 26, 1995.

Rejection Under 35 U.S.C. § 103 (a)

Claims 154-160 are rejected under 35 U.S.C. § 103 (a) as allegedly unpatentable over June et al., U.S. Patent No. 6,352,694 (hereinafter "June") in view of Hsieh et al. and Cracauer et al., U.S. Patent No. 4,804,628 (hereinafter "Cracauer") for reasons of record. In particular, the Examiner alleges that June discloses the expansion of cell to greater than 10^{10} cells while acknowledging that June lacks any teaching regarding the specific concentration claimed or the addition of anti-IL-4 antibody. According to the Examiner, Cracauer discloses the expansion of cells *in vitro* at concentrations greater than 10^{8} cells/ml while Hsieh discloses that neutralizing IL-4 with anti-IL-4 antibody resulted in the production of Th1 cells. Applicant traverses this rejection.

Applicant respectfully submits that the cited combination fails to teach or suggest the expansion of Th1 cells to at least about 10^{8} cells/ml, and thus fails to render the claimed methods

prima facie obvious. June discloses the expansion of T cells plated at densities of 0.5-2 x 10^6 cells/ml. *See, e.g.*, June at col. 33:39-50; col. 34:21-26; and col. 45:7-11. In fact, June specifically teaches maintaining the cell concentrations between 0.5-1.5 x 10^6 cell/ml during expansion to large numbers, teaching away from the instant methods where the cells are expanded to at least 10^8 cells/ml. *See* June at col. 45:7-11. Applicant notes that such teachings cannot be ignored. *See* MPEP § 2141.02 ("A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention.") (citations omitted).

Neither Cracauer nor Hsieh remedies this deficiency. Contrary to the assertion of the Examiner, Cracauer lacks any teaching regarding the use of hollow cell fiber to *expand* non-transformed lymphocyte populations. Cracauer discloses the use of the hollow cell fibers to maintain cells to "economically produce cell-derived products." *See* Cracauer at col. 1:50-54. In other words, Cracauer is directed to the generation of proteins, etc. produced by cells, not the cells themselves. Cracauer exemplifies the invention by describing the growth and maintenance of hybridoma cells, a transformed cell line, used to produce large quantities of monoclonal antibodies. *See* Cracauer at col. 5:57-61. However, the expansion and maintenance of transformed cells which require no additional stimulation for growth is distinct from the expansion of non-transformed cells requiring specific stimulation in order to expand a cell population with a particular functional phenotype. Thus, Cracauer fails to provide any indication regarding the ability of these hollow cell fibers to support a dynamic growth environment for non-transformed cells from patients are serially stimulated to maintain growth as well as specific functional properties. In fact, Cracauer is completely silent regarding the use of non-transformed cells or such dynamic conditions. Likewise, Hsieh is silent regarding expansion of normal lymphocytes to such high cell densities while retaining a particular functional profile. Furthermore, Hsieh simply discloses the use of IL-4 in modulating primary antigen stimulation using transgenic T cells. Results in transgenic mice do not necessarily predict the responses using human cells with both primary and memory cells and thus at best offers only a suggestion to try using IL-4 antibody. For at least these reasons, the cited combination of June, Cracauer, and Hsieh fail to teach each and every element of the claimed methods, therefore failing to render the claimed methods *prima facie* obvious.

In view of the above, the basis for the rejection may be removed.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 549172000112.

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Respectfully submitted,

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